Review

Diletta Onorato*, Giovanni Carpenè, Giuseppe Lippi and Mairi Pucci

Updated overview on the interplay between obesity and COVID-19

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Abstract: The worldwide spread of coronavirus disease 2019 (COVID-19) has generated a global health crisis and more than a million deaths so far. Epidemiological and clinical characteristics of COVID-19 are increasingly reported, along with its potential relationship with overweight and/or obesity. Therefore, we aim here to review the current scientific literature on the impact of overweight and/or obesity among hospitalized patients who have developed severe or critical forms of COVID-19. Following PRISMA guidelines, our literature search identified over 300 scientific articles using the keywords "obesity" and "COVID-19", 22 of which were finally selected for reporting useful information on the association between overweight/obesity and disease severity. In particular, in 11 out of the 14 studies (79%) which evaluated the association between obesity and disease severity providing also a risk estimate (i.e., the odd ratio; OR), the OR value was constantly >2. Although the studies were found to be heterogeneous in terms of design, population, sample size and endpoints, in most cases a significant association was found between obesity and the risk of progressing to severe COVID-19 illness, intensive care unit admission and/or death. We can hence conclude that an increased body mass index shall be considered a negative prognostic factor in patients with COVID-19, and more aggressive prevention or treatment shall hence be reserved to overweight and/or obese patients.

Keywords: coronavirus disease; COVID-19; obesity; review.

Introduction

In December 2019 a new virus belonging to the Coronaviridae family has been identified as the responsible pathogen of a new pneumonia-like illness [1]. This novel virus, which has been finally defined severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a zoonotic pathogen originated by spillover from bats in Wuhan, China, from where the infection has then spread all around the world [1]. SARS-CoV-2 belongs to the beta coronavirus subfamily, which is known for other similar viruses responsible of two previous epidemic diseases, i.e., the severe acute respiratory syndrome (SARS) in 2002 and the Middle-East respiratory syndrome (MERS) in 2012, respectively [2, 3]. SARS-CoV-2 rapidly spread from China, infecting Europe (with the first case in Italy on 28th February 2020), America, Australia and Africa. On the 11th March 2020 the pandemic state has been finally declared by the World Health Organization (WHO) [4].

SARS-CoV-2 is responsible of an illness that has been defined COVID-19, which is characterized by a heterogeneous spectrum of clinical manifestations, from asymptomatic disease to development of pulmonary involvement (with pneumonia and/or acute respiratory distress syndrome; ARDS), up to systemic dissemination with multiple organ failure and high risk of death [5]. The incubation period is typically comprised between 1 and 14 days. Although respiratory involvement is the most frequent complication in symptomatic people, this frequently needing mechanical ventilation and intensive care unit (ICU) admission, the first set of symptoms may include visual, olfactory, gastrointestinal and skin disturbances, encompassing also fever, headache, dry cough, fatigue, ageusia, anosmia and diarrhea [6].

The current figures of SARS-CoV-2 infection reveal that the virus has already infected nearly 43 millions of people worldwide, causing over 1.156.000 deaths [7]. Although the

Diletta Onorato and Giovanni Carpenè contributed equally to this work.

***Corresponding author: Diletta Onorato**, MD, Section of Clinical Biochemistry, Department of Neurosciences, Biomedicine and Movement Sciences Verona, Italy, Phone: ++39 045 8124512, Fax: ++0458124514, E-mail: dilettaonorato@gmail.com. https://orcid.org/0000-0002-6147-7115
Giovanni Carpenè, Giuseppe Lippi and Mairi Pucci, Section of Clinical Biochemistry, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy. https://orcid.org/0000-0001-9523-9054 (G. Lippi), https://orcid.org/0000-0001-7550-4893 (M. Pucci)

virus can virtually infect all individuals, with no clear distinction of sex, age and diseased status, the clinical progression seems to be strongly influenced by a number of demographic and clinical factors, which would need to be accurately and timely identified for providing the most accurate care to the patients according to their health condition and disease state [5]. In particular, the information garnered so far seemingly attests that elderly subjects are more vulnerable to COVID-19, and carry a higher risk of developing severe illness, being admitted to the ICU and dying [8]. Males are also more susceptible than females to progress towards severe COVID-19 illness [9], but the presence of some associated pathologies can substantially amplify the pathogenic potential of SARS-CoV-2 [10]. Notably, a number of studies have described worse clinical outcomes in COVID-19 patients with hypertension and diabetes [11–13]. These two chronic conditions are associated with endothelial injury and dysfunction, and would hence represent important predisposing factors for increased risk of mortality and morbidity. In a meta-analysis conducted by Li et al., 28.8% of COVID-19 patients in ICU had hypertension, while this proportion was only 14.1% in those not needing ICU care [14]. Similarly, Onder et al. reported an extraordinary prevalence of diabetes, as high as 35.5%, in 355 Italian patients who died for COVID-19 [15].

It has been now definitely established that SARS-CoV-2 enters the host cell by binding to the transmembrane enzyme angiotensin-converting enzyme 2 protein (ACE2), which is widely expressed in a variety of human tissues. In a recent analysis, Li et al. found that ACE2 is strongly expressed in the adipose tissue, at an even higher extent than in cells of lower respiratory tract [16]. The adipose tissue would hence represent a natural reservoir for SARS-CoV-2 [17], potentially increasing the overall systemic viral load and thereby the risk of unfavorable clinical progression [18]. On the other hand, it is also widely known that obesity, with excessive visceral fat, is associated with chronic inflammatory conditions and magnified release of pro-inflammatory cytokines into the bloodstream, which might then provide an important milieu for development or amplification of the paradigmatic "cytokine storm" observed in COVID-19 patients with severe illness [19]. Obese subjects have also decreased expiratory reserve volume, functional capacity and respiratory compliance, along with reduced diaphragmatic excursion and impaired pulmonary function in supine position, which would all contribute to make pulmonary ventilation very challenging in COVID-19 patients with severe pulmonary involvement [20].

These important aspects, combined with recent studies demonstrating that ACE2 is over-expressed in adipocytes, persuaded us to carry out a critical review of the current scientific literature on the impact of overweight and/or obesity among hospitalized patients at risk of developing severe or critical forms of COVID-19 [21].

Materials and methods

To perform our systematic review, we carried out an electronic search in Medline (PubMed interface) and Scopus, using the keywords "COVID-19" OR "SARS-CoV-2" OR "coronavirus 2019" AND "obesity" OR "overweight", up to 7th July 2020, applying a restriction to articles published in English and in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) guidelines [22]. The reference list of all documents was reviewed for identifying additional potentially eligible studies. The title, abstract and full text of the articles identified according to our search criteria were analyzed by two authors, and were considered eligible for inclusion in this literature review if they were case series (sample size >10) or observational studies reporting clear extractable data on body mass index (BMI) in laboratory-confirmed COVID-19 patients, and compared BMI between patients with severe or non-severe disease or between survivors and non-survivors. Reviews, case reports and other editorial material with no original data were excluded (Figure 1). Disagreement arising during the selection assessment were resolved by discussion and consensus. The data extracted included: authors, year of publication, country, type of study, number of patients, number of obese or overweight subjects, age, sex, BMI cut-off for obesity, outcome (death or severe infection), severe infection criteria (ICU admission, need for invasive mechanical ventilation, presence of at least one respiratory distress such as >30 breaths/min, Sat <93%, FIO2 defined as the ratio of partial pressure of oxygen and fraction of inspired oxygen ≤300 mmHg) and correlations between BMI and disease severity (Table 1).

Results

A total of 22 studies [21, 23–43] were finally selected out of over 300 scientific articles preliminarily identified according to our search criteria (Table 1). The cohorts of patients in these studies were extremely heterogeneous for ethnicity, age, comorbidities, degree of overweight/obesity and clinical outcome, so that performance of a meta-analysis was unfeasible. We decided to not compare all the studies as they were performed with different statistical methods which made impossible combine them and proceed with a statistically relevant analysis. Therefore, we limited our specific analysis to the 14 studies which evaluated the association between obesity and COVID-19 severity and reported a clear risk estimate (i.e., the odds ratio; OR). 11 of such investigations [21, 23–31, 38, 40, 41, 43] reported an OR value >2 (totaling 2058 total patients, 852 obese), two other studies reported an OR value <1 and the remaining investigation reported an intermediate value (Figure 2).

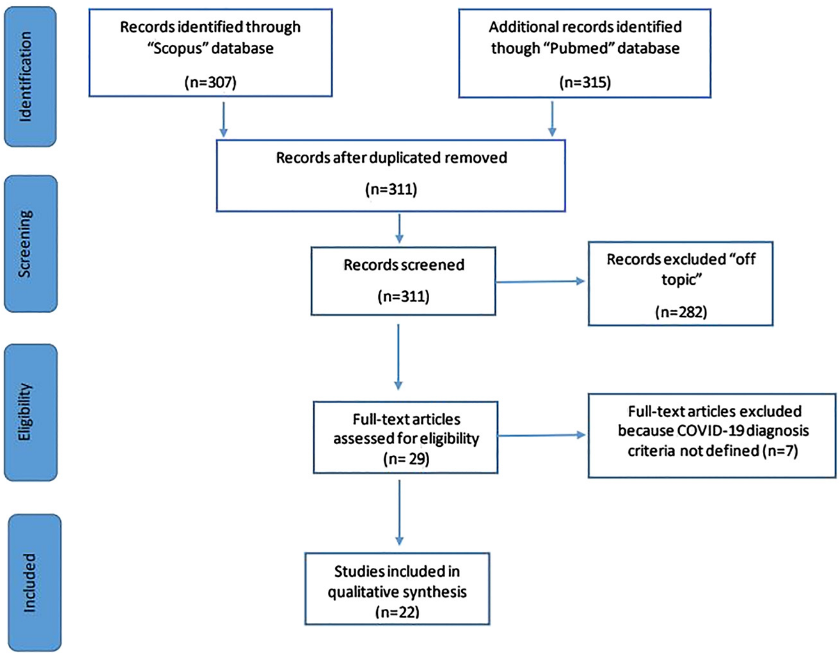

Figure 1: Flow diagram of the literature search and selection process in the systematic review.

The death rate as endpoint was evaluated in a limited number of studies. Pettit et al. [38] reported that obesity (defined as BMI>30 kg/m^2) was a significant predictor of death, with an OR of 1.7 (95% CI, 1.1–2.8). These findings were confirmed by Docherty et al. [36], who prospectively followed-up 20133 patients with COVID-19, and reported 33% increased risk of death in those with unspecified obesity (hazard ratio, 1.33; 95% CI, 1.19–1.49). In the analysis of Klang et al. [31], BMI >40 kg/m^2 was found to be independently associated with mortality, especially in the population aged <50 years (OR, 5.1; 95% CI, 2.3–11.1), whereas this association was found to be less pronounced in older subjects (aged 50 years or older; OR, 1.6; 1.2–2.3). Finally, Palaiodimos et al. [30] studied 200 COVID-19 patients and also found that a BMI>35 kg/m^2 was significantly associated with the risk of death (OR 3.78; 95% CI, 1.15–9.83).

Discussion

The aim of this article was to review the current scientific literature to identify clinical studies exploring the potential relationship between overweight/obesity and unfavorable COVID-19 progression. Although a broad heterogeneity was found in the investigations in terms of study design (some were prospective, others retrospective), sample size, ethnical origin, definition of overweigh/obesity, presence of co-morbidities and clinical endpoints (Table 1), a significant association between overweight and disease severity can be clearly seen. This would hence represent an important aspect that shall be considered when planning the most suitable preventive and therapeutic measures for managing patients with COVID-19, since overweight/obese patients may be especially vulnerable to the adverse consequences of SARS-CoV-2 infection.

Notably, ACE2 expression is higher in adipose tissue than in lower respiratory tract, and adipocytes shall hence be considered a major target of SARS-CoV-2 infection, as well as potential viral reservoirs [44, 45]. Obesity is also frequently accompanied by increased circulating levels of pro-inflammatory biomarkers such as interleukin 6 (IL-6) and C-reactive protein (CRP), thus underpinning the potential pro-inflammatory role of adipose tissue, characterized by enhanced expression of cytokines, which could ultimately contribute to induce lymphocytes apoptosis [21]. Interestingly, thrombotic episodes, either localized or disseminated, frequently complicate severe SARS-CoV-2 infections, even in patients undergoing systemic anticoagulation therapy [46, 47]. Since obesity has been consistently associated with an increased risk of developing venous thromboembolism [48], the prothrombotic potential of obesity shall be considered another reasonable mechanism to explain unfavorable progression of COVID-19. Finally, obesity is associated with a globally impaired pulmonary function, which may ultimately render overweight or frankly obese COVID-19 patients less responsive to mechanical ventilation used for managing respiratory distress [20, 49].

In conclusion, the results of this critical literature review would contribute to confirm that overweight and/or

Table 1: Description of the main studies that considered obesity as a risk factor for COVID-19.

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/overweight and disease severity OR	Conclusions
Caussy C. et al. [23]	France	Cohort prospective	340 (in Lyon ICU)	85	Average age ≥65 years	197/340	BMI >30	Admitted in intensive care unit	Severe disease	OR: 2.05 [1.24, 3.41] P-Value 0.006	Significant association between the prevalence of obesity and severe COVID-19
Simonnet A. et al. [24]	France	Single center, retrospective cohort study	124	BMI>30: 59; BMI≥35: 35	Median age was 60 years	90/124	Overweight: BMI 25–30; Obesity: BMI >30; Severe obesity: BMI ≥35	Requirement for invasive mechanical ventilation (IMV)	Severe disease	OR for IMV in patients with BMI >35 vs. patients with BMI <25 was 7.36 (1.63–33.14; p=0.02)	Disease severity increased with BMI. Obesity is a risk factor for SARS-CoV-2 severity
Kalligeros M. et al. [25]	USA	Retrospective cohort	103	BMI 25–29.9: 35; BMI 30–34.9: 22; BMI ≥35: 27	Median age was 60 years	63/103	Obesity BMI >30; s Severe obesity BMI ≥35	Admitted in intensive care unit (ICU); Requirement for invasive mechanical ventilation (IMV)	Severe disease	OR ICU admission: 2.80 (0.75–10.48) P-Value 0.126 if BMI 30–34.9 and OR 3.02 (0.85–10.74) P-Value 0.088 if BMI ≥35 OR requirement IMV: 4.86 (0.88–26.68) P-Value 0.069 if BMI 30–30.49 and 5.84 (1.12–30.55) P-Value 0.036 if BMI≥35	Severe obesity (BMI ≥35) was associated with ICU admission, while history of heart disease and obesity (BMI ≥30) were independently associated with the use of IMV
Gao F. et al. [26]	China	Retrospective multicenter cohort study	150	Not specified	Averageage was 48 years	94/150	BMI >25	Presence of at least one respiratory distress (>30 breaths/min, Sat <93%, FIO2<300)	Severe disease	Or: 2.91 (95% CI 1.31–6.47)	Obesity increases the risk of severe illness approximately threefold with a consequent longer hospital stay

Table 1: (continued)

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/overweight and disease severity OR	Conclusions
Petrilli CM. et al. [27]	USA (New York)	Prospective cohort study	5279	BMI 25.0–29.9: 1769 BMI 30.0–39.9: 1554 BMI ≥40 311	Median age was 54 years old	2615/5279	Obese BMI 30–39.9 Super obese BMI ≥40	Critical illness (intensive care, mechanical ventilation, discharge to hospice care, or death)	Severe disease	OR 0.73 (0.59–0.90) if BMI 30–39.9 OR 0.87 (0.63–1.22) if BMI ≥40	The strongest risks for critical illness besides age were associated with heart failure (1.9, 1.4 to 2.5), BMI >40 (1.5, 1.0 to 2.2), and male sex (1.5, 1.3 to 1.8)
Cai Q. et al. [28]	China (Shenzen)	Single center, prospective study	383	Overweight 123; Obese 41	18–62	183/383	Overweight BMI 27-27,9 O Obesity >28	Presence of (almost one) respiratory distress (>30 breaths/min), Sat <93%, FIO2<300)	Severe disease	BMI adjusted for age: BMI 24–27.9: 1.78 (1.00–3.21) P-Value 0.05 BMI >28: 3.35 (1.47–7.63) P-Value 0.004 Multivariate: BMI 24–27.9: 1.84 (0.99–3.43) P-Value 0.05. BMI >28: 3.40 (1.40–8.26) P-Value 0.007	Obese patients had increased odds of progressing to severe COVID-19
Huang R. et al. [29]	China (Jiangsubprovince)	Multi-center, retrospective study	202	24	Average age 44 years	116/202	BMI >28	Presence of at least one respiratory distress (>30 breaths/min, Sat <93%, FIO2<300)	Severe disease	Univariate: 6.900 (2.381, 19.997) P-Value <0.001; Multivariate: 9.219 (2.731, 31.126) P-Value <0.001	The study provides a comprehensive description of the clinical characteristics of laboratory confirmed cases of COVID-19, and the risk factors for severe COVID-19

Table 1: (continued)

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/overweight and disease severity OR	Conclusions
Palaiodimos L. et al. [30]	USA (Bronx- New York)	Retrospective study	200	BMI 25–34: 116; BMI≥35: 46	Median 64 years	98/200	Overweight 25–34; Obesity ≥35	In-hospital mortality; Increasing oxygen requirement during hospital stay; Intubation	Death and severe disease	BMI ≥35 mortality: OR: 3.78; 95% CI: 1.45–9.83; p=0.006; B Oxygen requirement in BMI ≥ 35 OR: 3.09; 95% CI: 1.43–6.69; p =0.004; Intubation: in BMI≥35 OR: 3.87; 95% CI: 1.47–10.18; p=0.006	BMI ≥ 35 were found to have significant associations with mortality, increase oxygen requirement, intubation
Klang E. et al. [31]	USA (New York)	Retrospective color study	572	240	Average age 64 years	352/572	BMI ≥ 30	Death; Intubation, mechanical ventilation	Death and severe disease	Mortality: <50 years-BMI >40 OR 5.1, 95% CI 2.3–11.1; Mortality>50 years -BMI ≥ 40 OR 1.6, 95% CI 1.2–2.3; Intubation and mechanical ventilation: BMI ≥ 40 both in the young age group (OR 4.1, 95% CI 2.1–8.2) OR in the older age group (OR 1.5, 95% CI 1.1–2.1)	For the younger population, BMI above 40 kg/m2 was independently associated with mortality; for older population, BMI ≥ 40, was also independently associated with mortality; secondary outcome, intubation and mechanical ventilation status was independently Associated with BMI ≥ 40 both in the young age group and in the older age group

Table 1: (continued)

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/ total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/ overweight and disease severity OR	Conclusions
Buckner FS. et al. [32]	USA (Seattle)	Retrospective study	105	44	Median 69 years	53/105	BMI >30	Admission to an intensive care unit (ICU) or death, shock and acute respiratory distress syndrome (ARDS)	Death and severe disease	Not specified	Correlation between obesity and severe clinical outcomes
Urra JR. et al. [21]	Spain	Retrospective case-control study	172	17	44–79 years old	104/172	BMI >30	Admission to intensive care unit (ICU)	Severe disease	Univariate OR = 4.72 (95% CI 1.614–13.830), p=0.005	Obesity predict a poor prognosis in patients with covid19 disease.
Zachriah P. et al. [33]	USA (New York)	Retrospective study	50	Obese: 11, overweight: 8	<21 years old	27/50	Obese: BMI at or above the 95th percentile for age/sex; Overweight: BMI between 85 and 95th percentile for age/sex	Requirement for mechanical ventilation	Severe disease	Among patients with non severe-disease 20% were obese. Among patients with severe-disease 67% were obese	Obesity was the most significant factor associated with mechanical ventilation in children 2 years and older
Bello-Chavolla OY. et al. [34]	Mexico	Retrospective study	51633	10708	Averageage 46 years	29.803/ 51633	Not specified	Death, admission to intensive care unit (ICU), intubation	Death and severe disease	Univariable HR: 1.25 (1.17–1.34, p<0.001)	Confirmed covid-19+ cases with obesity had higher rates for ICU admission, need for intubation and mortality. Obese mediates 49,5 of the effect of diabetes on COVID-19 lethality.
Cummings MJ. et al. [35]	USA (New York)	Prospective observational cohort study	257	Obese 119, super obese 33	Average age 62 years	171/257	Obese: BMI>30 Super obese: BMI>40	Frequency and duration of invasive mechanical ventilation,	Death and severe disease	Univariable HR for BMI>40 0.76 (0.40–1.47)	46% of critically ill patients had obesity. BMI>40 hasn't identified

Table 1: (continued)

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/overweight and disease severity OR	Conclusions
								frequency of vasopressor use and renal replacement therapy, time to in-hospital clinical deterioration following admission			as an independent risk factor for mortality. Obesity is associated with mortality in hospital
Docherty AB. et al. [36]	UK	Prospective observational cohort study	20133	1671	Average age 73 years	12068/20133	Not specified	Admission to critical care and mortality in hospital	Death and severe disease	Univariable HR: 0.91 (0.82–1.01,p=0.077); Multivariable HR: 1.33 (1.19–1.49, p<0.001)	Obesity is associated with mortality in hospital in COVID + patients
Dreher M. et al. [37]	Germany	Cohort retrospective study	50	17	Average age 65 years	33/50	BMI ≥ 30	Presence of al least one respiratory distress symtoms (>30 breaths/min, Sat <93%, FIO2<300)	Severe disease	Among patients with ARDS 46% were obese (vs. 23% in patients without ARDS).Prevalence overweight (38 vs. 19%)	Correlation between obesity and severe clinical outcomes
Pettit NN. et al. [38]	USA (Chicago)	Retrospective cohort study	238	146	Average age 58.5 years	113/238	BMI >30	Death; Hypoxemia	Death and severe disease	Mortality OR: 1.7(1.1–2.8), p=0.016 in multivariable analysis. Hypoxemia OR: 1.7(1.3–2.1),p<0.0005) in multivariable analysis	Obesity was identified as a predictor for mortality, as was male gender and older age and older were also risk factors for hypoxemia
Hu X. et al. [39]	China	Single-center, retrospective study	55	55	Averageage 49.2 years	36/55	BMI ≥24	Prolonged hospitalization (more than the median value of the hospitalized days in this population)	Severe disease	BMI HR = 0.83, P for trend = 0.001	BMI and ALT were inversely associated with being discharged from hospital in time, respectively

Table 1: (continued)

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/ total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/ overweight and disease severity OR	Conclusions
Busetto L. et al. [40]	Italy	Retrospective cohort	92	Obese: 29 Overweight: 31;	Averageage 70.5 years	57/92	BMI ≥25	Need for assisted ventilation beyond pure oxygen support (Invasive mechanical ventilation or Non-Invasive ventilation) SEMI + ICUs vs medical ward	Severe disease	OR NIV + IMV vs. only oxygen: 4.19 (1.36–12.89) p0.012. OR SEMI + ICUs vs. medical ward: 11.65 (3.88–34.96) p<0.001	Patients with overweight and obesity required more frequently assisted ventilation and access to intensive or semi-intensive care units than normal weight patients
Zheng KI. et al. [41]	China	Prospective study	66	45	18–75 years old.	49/66	BMI>25	Presence of at least one respiratory distress (>30 breaths/ min, Sat <93%, FIO2<300)	Severe disease	OR unadjusted: 5.77 (1.19–27.91) P-Value 0.029. OR adjousted for age and sex: 6.25 (1.23–31.71) P-Value 0.027 OR adjousted for age, sex, smoking, type 2 DM, hypertension, dyslidemia: 6.32 (1.16–34.54) P-Value 0.033	Compared to those with non-severe COVID-19, patients with severe disease were more obese
Goyal P. et al.[42]	USA (New York)	Multi-center, retrospective study	393	136	Median 62.2 years	238/393	BMI >30	Mechanical ventilation	Severe disease	Not specified	43.4% of patients who received invasive mechanical ventilation were obese

Table 1: (continued)

Study ID	Country	Type of study	Number of patients COVID-19+	Number of obese or overweight patients	Age	Male/total	BMI cut-off for obesity	Severe infection criteria	Outcomes	Correlations between obesity/overweight and disease severity OR	Conclusions
Lighter J. et al. [43]	USA (New York)	Retrospective study	3615	BMI 30–34: 96; BMI ≥35:106.	<60 years old ≥60 years old	Not specified	Obese BMI 30–34; super obese BMI ≥35	ICU admission.	Severe disease	Age ≥60 years: OR 1.1 (95% CI 0.8–1.7) P-Value 0.57 with BMI 30–34 OR 1.5 (95% CI 0.9–2.3) P-Value 0.10 with BMI ≥35.Age <60 years: OR 1.8 (95% CI 1.2–2.7) P-Value 0.006 with BMI 30-34 OR 3.6 (95% CI 2.5–5.3) P-Value <0.0001 with BMI ≥35	In patients aged <60 years old, obesity appears to be arisk factor for hospital admission and need for critical care

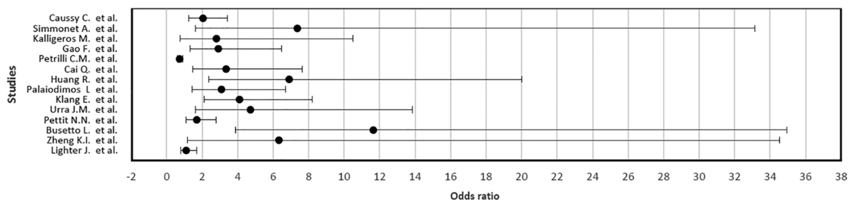

Figure 2: Confidence intervals of the ORs evaluated in the main studies for severe disease.

obesity seem to have a substantial impact on the risk of developing severe/critical SARS-COV-2 infections, so that overweight/obese COVID-19 patients shall be targeted with more aggressive preventive or therapeutic measures to prevent unfavorable outcomes. Further studies shall also be planned to investigate the interplay between low BMI and the pathogenesis of COVID-19.

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